CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074864

Trade Name : RANITIDINE TABLETS USP

Generic Name: Ranitidine Tablets USP 150mg and 300mg (present as the hydrochloride)

Sponsor : Chelsea Laboratories, Inc.

Approval Date: October 20, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074864

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074864

APPROVAL LETTER

ANDA 74-864

OCT 20 1997

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
P.O. Box 15686
8606 Reading Road
Cincinnati, OH 45215

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 29, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Tablets USP, 150 mg and 300 mg (present as the hydrochloride).

Reference is also made to your amendment dated July 29 and October 1, 1997.

The listed drug product referenced in your application is subject to a period of patent protection which expire on June 4, 2002, (patent 4,521,431) and May 13, 2008 (patent 4,880,636). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of ranitidine hydrochloride will not infringe on the patent or that the patent is otherwise invalid. You further informed the Agency that Glaxo, Inc. initiated a patent infringement suit against you in the United States District Court Western District of North Carolina(Glaxo Wellcome, Inc. and Glaxo Group Limited v. Chelsea Laboratories, Inc. and Hoechst Marion Roussel Inc., Civil Action No. 3:96CV208MU). On October 1, 1997, you notified the Agency that a Settlement Agreement between the plaintiffs and the defendants was signed on September 30, 1997. The Agreement states that the parties have terminated the litigation referenced above.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The Division of Bioequivalence has determined your Ranitidine Tablets USP, 150 mg and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zantac Tablets, 150 mg and 300 mg, respectively, of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method

proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

10/20/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074864

TENTATIVE APPROVAL LETTER

ANDA 74-864

JUL 24 1997

Chelsea Laboratories, Inc.
Attention: Ernie E. Lengle, Ph.D.
8606 Reading Road
Cincinnati, Ohio 45215

Dear Sir:

This is in reference to your abbreviated new drug application dated February 29, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ranitidine Tablets USP, 150 mg and 300 mg (present as the hydrochloride). The application contains patent certifications under section 505(j)(2)(A)(vii)(III and IV) of the Act.

Reference is also made to your amendment dated July 21, 1997.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, which includes information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products. Therefore, this determination is subject to change on the basis of new information that may come to our attention. This letter addresses issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to periods of patent protection which expire on July 25, 1997 (patent 4,128,658), June 4, 2002 (patent 4,521,431), and May 13, 2008 (patent 4,880,636). However, you have informed us that litigation is underway in the United States District Court Western District of North Carolina, involving a challenge only to the patent 4,521,431 (Glaxo Wellcome, Inc. and Glaxo Group Limited v. Chelsea Laboratories, Inc. and Hoechst Marion Roussel Inc., Civil Action No. 3:96CV208MU).

The Agency has reviewed the application of the 180-day exclusivity provisions of the Act to the ANDAs submitted for ranitidine. FDA's regulations interpreting these provisions are set out at 21 CFR 314.107(c). The U.S. District Court for the

District of Columbia has recently held that the Agency's interpretation of the 180-day exclusivity provisions is inconsistent with the Act, and found invalid the Agency's position that in order to qualify for 180 days of exclusivity the first ANDA applicant with a paragraph IV certification must be sued and prevail in patent infringement litigation. Mova Pharmaceuticals v. Kessler, 955 F. Supp. 128 (D.D.C. 1997). See also Inwood Laboratories, Inc. v. Young, 723 F. Supp. 1523 (D.D.C. 1989), vacated as moot, 43 F.3d 712 (D.C. Cir. 1989). The court determined that the Act requires exclusivity be granted to the first ANDA submitted with a paragraph IV certification to a patent, regardless of whether such certification results in litigation or whether the applicant prevails in the litigation. Until such time as the decision is reversed on appeal, FDA will acquiesce in the Mova decision.

In the case of approval of ANDAs for ranitidine, Mova dictates that Genpharm Inc., as the first ANDA applicant with a paragraph IV certification to the patents listed for the reference drug, receive 180 days of exclusivity. The Act [21 U.S.C. § 355(j)(4)(B)(iv)] provides that a subsequent application shall be made effective not earlier than one hundred and eighty days after:

> (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court in action described in clause [505(j)(4)(b)(iii)] holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

The Agency interprets this provision as triggering the beginning of the 180-day exclusivity period with a decision of any court in a patent infringement action related to a paragraph IV certification finding the patent invalid or not infringed, whether or not it is the court hearing a patent infringement action resulting from the first paragraph IV certification.

The first decision of a court in an action resulting from a paragraph IV certification to a patent listed for ranitidine holding the patent invalid or not infringed was in the case involving Boehringer-Ingelheim. In that case, the District Court for Connecticut granted partial summary judgement on October 7, 1996, finding that the Boehringer-Ingelheim product (Form I) does not infringe the Form II patent (patent 4,521,431). The court ruled on other claims in the case on November 18, 1996. Final judgement was entered on January 31, 1997.

FDA regulations describe that the 180-day period will begin running from "the date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed." 21 CFR 314.107(c)(1)(ii). The relevant date of final decision of a court on patent issues is defined in 21 CFR 314.107(e)(2)(I) as follows:

> If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is not appealed, the date on which the right to appeal lapses.

In the case involving Boehringer-Ingelheim, the right to appeal did not lapse until March 3, 1997. Glaxo did not appeal the October 7, 1996 ruling. The 180 day period began on March 3, 1997, and will expire on August 29, 1997. It is important to note that the FDA will not approve an ANDA prior to the expiration of exclusivity notwithstanding a licensing agreement. This is explained in the preamble to the final rule, where the Agency states that licensees are subject to the 180-day exclusivity period [59 Fed. Reg. 50338, 50346, 50353 (Oct.3, 1994)].

Final approval of your application cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(4)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of court decision finding the patent invalid or not infringed [505(j)(4)(B)(iii)(I)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

   c. the latest expiring patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Ms. Kassandra C. Sherrod, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,

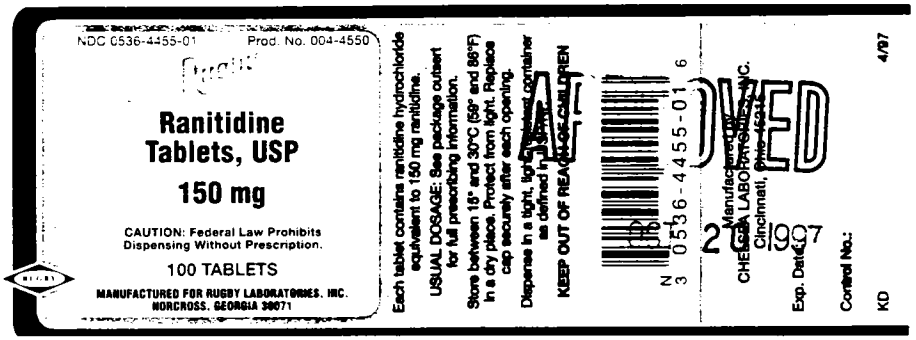
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

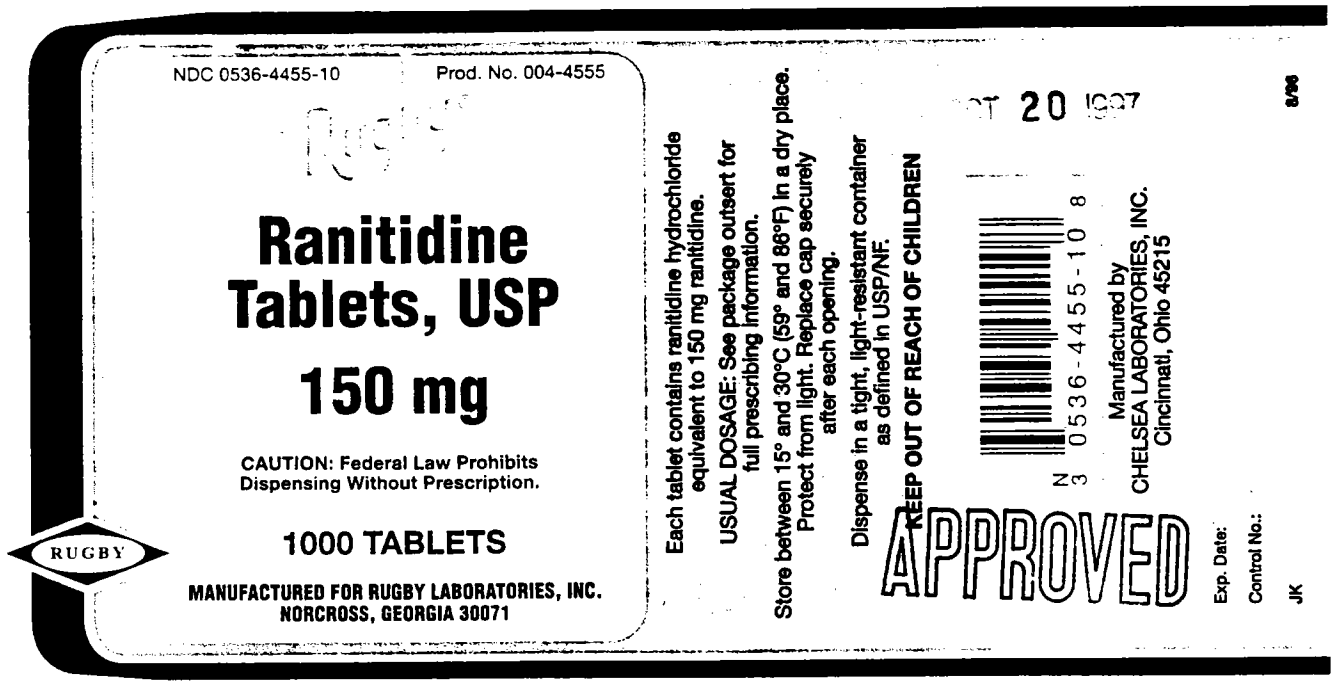
APPLICATION NUMBER 074864

FINAL PRINTED LABELING

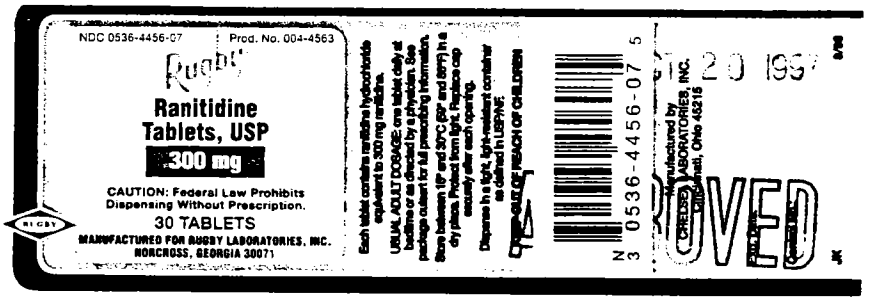
150 mg/ 100's
NDC 0536-44550-01
Plate code KD



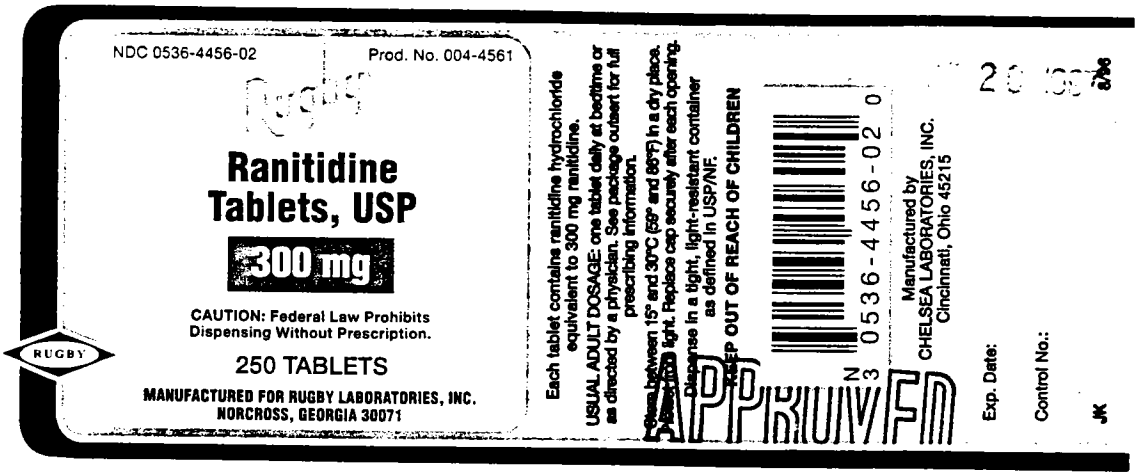
150 mg/1000's
NDC 0536-4455-10
Plate Code JK



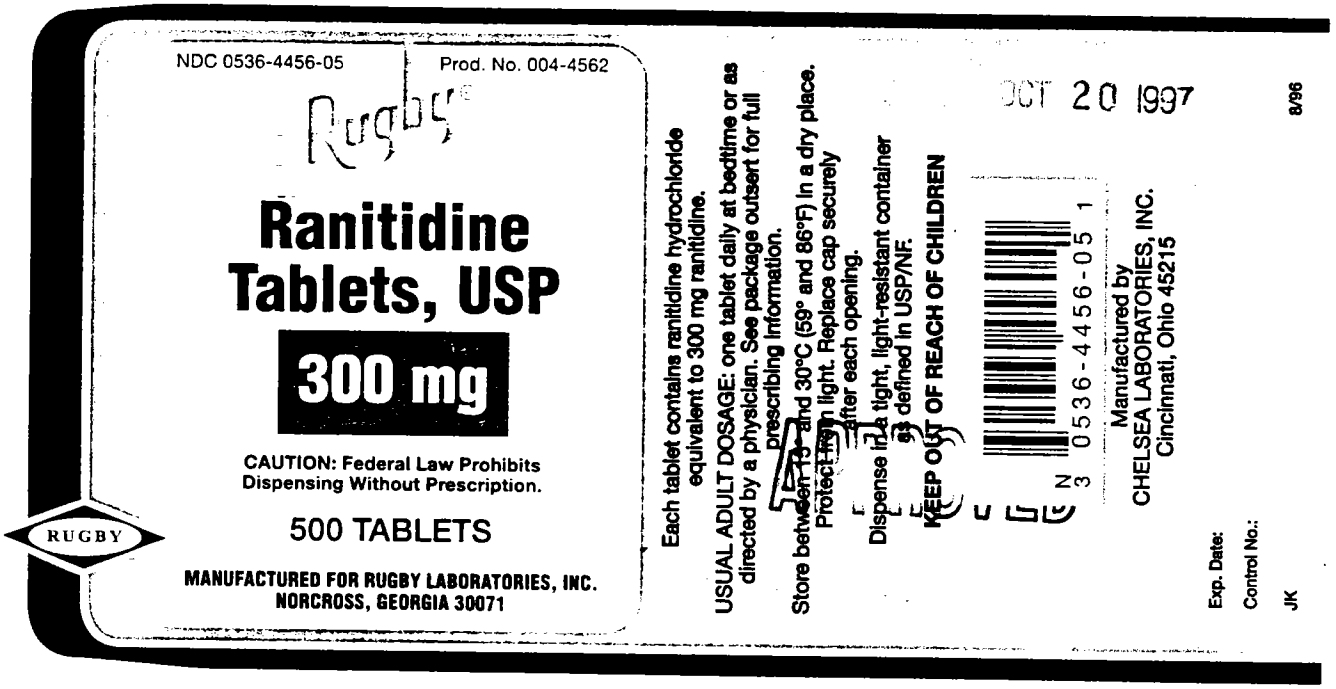
300 mg/30's
NDC 0536-4456-07
Plate Code JK



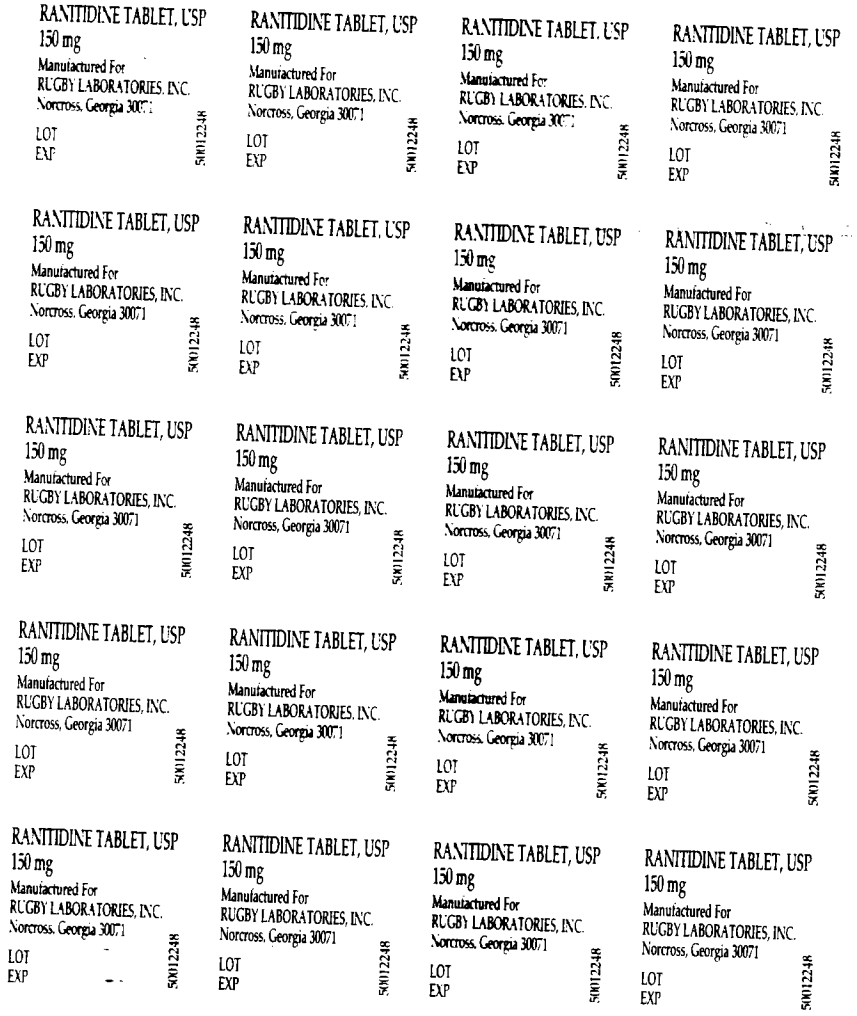
300 mg/250's
NDC 0536-4456-02
Plate Code JK



300 mg/500's
NDC 0536-4456-05
Plate Code JK



150 mg/ 100 unit dose strips
NDC 0536-4455-21
Plate Code 50012248



Note to the Reviewer:
The labeling component supplied here is the final proof from the printer. Actual foil lidding will be provided for review prior to the brand's patent expiration.

Chelsea Laboratories, Inc.

Ranitidine Tablets, USP Form 1

150 mg/100 unit dose carton
NDC 0536-4455-21
Plate Code 50012279

Usual Dosage: See package outsert for full prescribing information.
Store between 15° and 30°C (59° and 86°F) in a dry place.
This package intended for institutional use only.

N 3 0536-4455-21 4

Manufactured by CHELSEA LABORATORIES, INC.
CINCINNATI, OH 45215
Manufactured for RUGBY LABORATORIES, INC.
NORCROSS, GA 30071

NDC 0536-4455-21

Rugby®

Prod. No. 004-4556

RANITIDINE
TABLETS, USP
150 mg

Each tablet contains ranitidine hydrochloride equivalent to 150 mg ranitidine.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

100 UNIT DOSE TABLETS

NDC 0536-4455-21

Rugby®

Prod. No. 004-4556

RANITIDINE
TABLETS, USP
150 mg

Each tablet contains ranitidine hydrochloride equivalent to 150 mg ranitidine.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

100 UNIT DOSE TABLETS

RUGBY

NDC 0536-4455-21

Rugby®

Prod. No. 004-4556

RANITIDINE
TABLETS, USP
150 mg

Each tablet contains ranitidine hydrochloride equivalent to 150 mg ranitidine.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

000083

Exp. Date:

Control No:

USUAL ADULT DOSAGE: One tablet daily at bedtime or as directed by a physician. See package outsert for full prescribing information.

Store between 15° and 30°C (59° and 86°F) in a dry place.

This package intended for institutional use only.

Manufactured by CHELSEA LABORATORIES, INC.
CINCINNATI, OH 45215
Manufactured for RUGBY LABORATORIES, INC.
NORCROSS, GA 30071

NDC 0536-4456-21

Rugby®

RANITIDINE

TABLETS, USP

300 mg

100 UNIT DOSE TABLETS

50012249

NDC 0536-4456-21 Prod. No. 004-4566

Rugby®

RANITIDINE

TABLETS, USP

300 mg

Each tablet contains ranitidine hydrochloride equivalent to 300 mg ranitidine.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

100 UNIT DOSE TABLETS **UNIT DOSE**

NDC 0536-4456-21 Prod. No. 004-4566

Rugby®

RANITIDINE

TABLETS, USP

300 mg

Each tablet contains ranitidine hydrochloride equivalent to 300 mg ranitidine.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

RUGBY

100 UNIT DOSE TABLETS **UNIT DOSE**

NDC 0536-4456-21 Prod. No. 004-4566

Rugby®

NDC 0536-4456-21

Rugby®

50012249

50012249

1 3 4
5 6 7 8

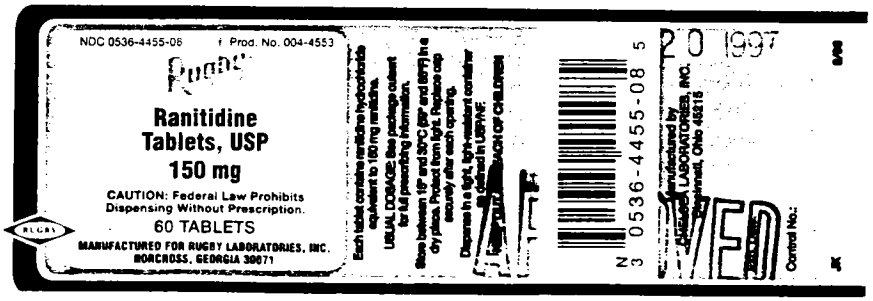
RANITIDINE

TABLETS, USP

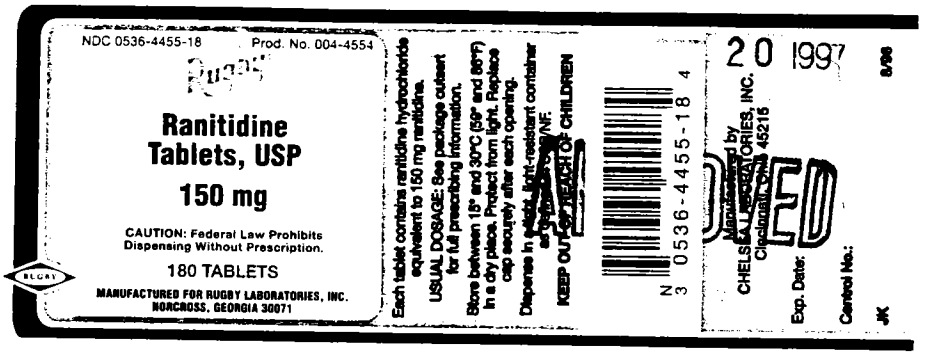
300 mg

100 UNIT DOSE TABLETS

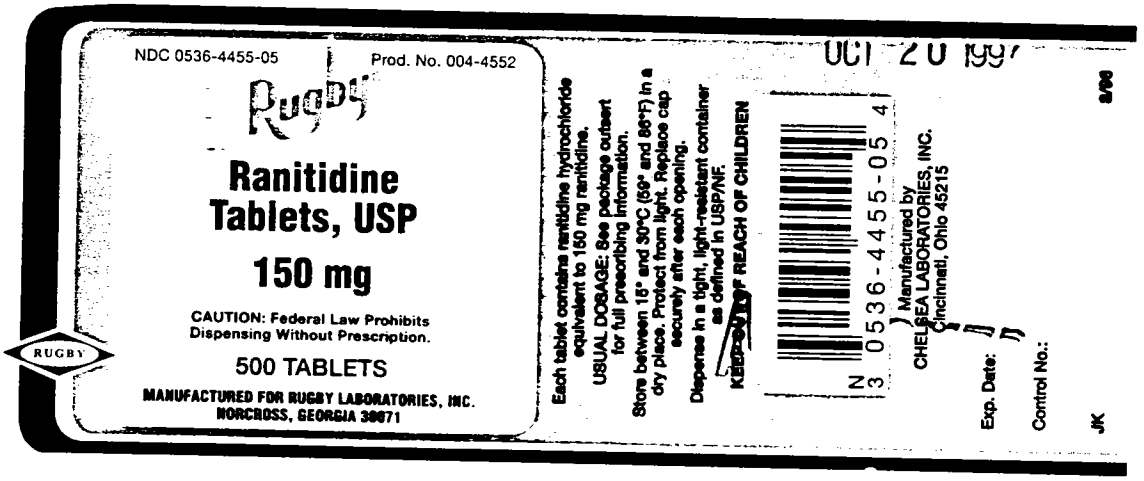
150 mg/60's
NDC 0536-4455-08
Plate Code JK



150 mg/180's
NDC 0536-4455-18
Plate Code JK



150 mg/500's
NDC 0536-4455-05
Plate Code JK



RANITIDINE TABLETS, USP

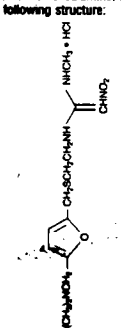
JK

JK

RANITIDINE TABLETS, USP

DESCRIPTION:

Ranitidine hydrochloride (HCl) is a histamine H_2-receptor antagonist. Chemically it is *N* [2- [[[5 - [(dimethylamino) methyl] -2- furanyl]methyl]thio]ethyl] -N' -methyl -2-nitro-1, 1-ethenediamine, HCl. It has the following structure:



The molecular formula is $C_{13}H_{22}N_4O_3S$·HCl, representing a molecular weight of 350.87.

Ranitidine HCl is a white to pale yellow, granular substance that is soluble in water. It has a slightly bitter taste and sulfur-like odor.

Each tablet, for oral administration, contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine, or 336 mg of ranitidine HCl equivalent to 300 mg of ranitidine. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, maltodextrin, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium bicarbonate, synthetic red iron oxide, synthetic yellow iron oxide, talc, titanium dioxide and triethyl citrate.

CLINICAL PHARMACOLOGY:

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca^{++} in hypercalcemic states. Ranitidine is not an anticholinergic agent.

Antisecretory Activity:

1. ***Effects on Acid Secretion:*** Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in the following table:

Oral Ranitidine on Gastric Acid Secretion					
er Dose,	% Inhibition of Gastric Acid Output by Dose, mg				
	75-80	100	150	200	
to 4		99	95		
o 13	95	96	92		
to 3		97	99		80
to 5	58	72	72		95
to 3		73	79		

vlene glycol, sodium bicarbonate, synthetic red iron oxide, synthetic yellow iron oxide, talc, titanium dioxide and triethyl citrate.

CLINICAL PHARMACOLOGY:

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca^{++} in hypercalcemic states. Ranitidine is not an anticholinergic agent.

Antisecretory Activity:

1. ***Effects on Acid Secretion:*** Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in the following table:

Effect of Oral Ranitidine on Gastric Acid Secretion

	Time After Dose, h	% Inhibition of Gastric Acid Output by Dose, mg				
		75-80	100	150	200	
Basal	Up to 4	95	96	95		
Nocturnal	Up to 13		99	92		
Betazole	Up to 3		97	99		
Pentagastrin	Up to 5	58	72	72	80	
Meal	Up to 3		73	79	95	

It appears that basal-, nocturnal-, and betazole- stimulated secretions are most sensitive to inhibition by ranitidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. ***Effects on Other Gastrointestinal Secretions:***

Pepsin: Oral ranitidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:

a. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.

b. Prolactin levels—no effect in recommended oral or intravenous (IV) dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

c. Other pituitary hormones—no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No antiandrogenic action.

f. No effect on count, motility, or morphology of sperm.

Pharmacokinetics:

Ranitidine is 50% absorbed after oral administration, compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring at 2 to 3 hours after a 150-mg dose. The elimination half-life is 2.5 to 3 hours.

Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL per minute, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL per minute) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8

Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL per minute, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL per minute) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL per minute, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

In man, the N-oxide is the principal metabolite in the urine; however, this amounts to < 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	195	69/182 (38%) †	188	31/164 (19%)
Week 4		137/187 (73%) †		76/168 (45%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$p < 0.0001$

In these studies patients treated with ranitidine reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Mean Daily Doses of Antacid	
	Ulcer Healed	Ulcer Not Healed
Ranitidine	0.06	0.71
Placebo	0.71	1.43

Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and 300 mg h.s. (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg b.i.d. as compared to 300 mg h.s. (92% versus 87%, respectively).

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose

acute duodenal ulcers in two independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers observed was significantly less in patients treated with ranitidine (150 mg h.s.) than in patients treated with placebo over a 12-month period.

Duodenal Ulcer Prevalence

Double-blind, Multicenter, Placebo-Controlled Trials							
Multicenter Trial	Drug	Duodenal Ulcer Prevalence					Number of Patients
		0-4 Months		0-8 Months		0-12 Months	
USA	RAN	20%*		24%*		35%*	138
	PLC	44%		54%		59%	139
Foreign	RAN	12%*		21%*		28%*	174
	PLC	56%		64%		68%	185

%=Life table estimate
***=$p \leq 0.05$ (Ranitidine versus comparator).**
RAN=ranitidine
PLC=placebo

As with other H_2-antagonists, the factors responsible for the significant reduction in the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid healing of ulcers that may occur during maintenance therapy, or both.

Gastric Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed gastric ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients Week 2	92	18/83 (19%)	94	10/83 (12%)
Week 6		50/73 (68%) †		35/69 (51%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$p = 0.009$

In this multicenter trial, significantly more patients treated with ranitidine became pain-free during therapy.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): Ranitidine inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative, "short-gut" syndrome, idiopathic). Use of ranitidine was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

Gastroesophageal Reflux Disease (GERD): In two multicenter, double-blind, placebo-controlled, 6-week trials performed in the United States and Europe, ranitidine 150 mg b.i.d. was more effective than placebo for the relief of heartburn and other symptoms associated with GERD. Ranitidine-treated patients consumed significantly less antacid than did placebo-treated patients.

The US trial indicated that ranitidine 150 mg b.i.d. significantly reduced the frequency of heartburn attacks and severity of heartburn pain within 1 to 2 weeks after starting therapy. The improvement was maintained throughout the 6-week trial period. Moreover, patient response rates demonstrated that the effect on heartburn extends through both the day and night time periods.

In two additional U.S. multicenter, double-blind, placebo-controlled, 2-week trials, ranitidine 150 mg b.i.d. was shown to provide relief of heartburn pain

conditions (e.g., post-operative, "short-gut" syndrome, idiopathic). Use of ranitidine was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

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In two additional U.S. multicenter, double-blind, placebo-controlled, 2-week trials, ranitidine 150 mg b.i.d. was shown to provide relief of heartburn pain within 24 hours of initiating therapy and a reduction in the frequency and severity of heartburn.

Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg q.i.d. was significantly more effective than placebo in healing endoscopically diagnosed erosive esophagitis and in relieving associated heartburn. The erosive esophagitis healing rates were as follows:

Erosive Esophagitis Patient Healing Rates

	Healed/Evaluable	
	Placebo* n=229	Ranitidine 150 mg q.i.d.* n=215
Week 4	43/198 (22%)	98/206 (47%)†
Week 8	63/176 (36%)	142/200 (71%)†
Week 12	92/159 (58%)	162/192 (84%)†

*All patients were permitted p.r.n antacids for relief of pain.
†$P < 0.001$ versus placebo.

No additional benefit in healing

of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg q.i.d.

INDICATIONS AND USAGE:

Ranitidine tablets are indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.

2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.

3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).

4. Short-term treatment of active benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.

5. Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after starting therapy with ranitidine 150 mg b.i.d.

6. Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg q.i.d.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS:

Ranitidine is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients (see PRECAUTIONS).

PRECAUTIONS:

General:

1. Symptomatic response to ranitidine therapy does not preclude the presence of gastric malignancy.

2. Since ranitidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine is metabolized in the liver.

3. Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests:

False-positive tests for urine protein with Multistix® may occur during ranitidine therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions:

Although ranitidine has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ranitidine may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.

Pregnancy:

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.

Pregnancy:

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

Ranitidine is secreted in human milk. Caution should be exercised when ranitidine is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Use in Elderly Patients:

Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS:

The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ranitidine administration.

Central Nervous System:

Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular:

As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal:

Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic:

In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal:

Rare reports of arthralgias and myalgias.

Hematologic:

Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine:

Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not

g.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

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Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

Integumentary:

Rash, including rare cases of erythema multiforme, and, rarely, alopecia.

Other:

Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE:

There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of ranitidine in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Active Duodenal Ulcer:

The current recommended adult oral dosage of ranitidine for duodenal ulcer is 150 mg twice daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated. (see CLINICAL PHARMACOLOGY, Clinical Trials: *Active Duodenal Ulcer*). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150-mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Maintenance of Healing of Duodenal Ulcers:

The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome):

The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ranitidine 150 mg dosages more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.

Benign Gastric Ulcer:

The current recommended adult oral dosage is 150 mg twice a day.

GERD:

The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis:

The current recommended adult

Benign Gastric Ulcer:
The current recommended adult oral dosage is 150 mg twice a day.

GERD:
The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis:
The current recommended adult oral dosage is 150 mg four times a day.

Dosage Adjustment for Patients with Impaired Renal Function:
On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine, the recommended dosage in patients with a creatinine clearance < 50 mL per minute is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED:
Ranitidine Tablets, USP (each tablet contains ranitidine hydrochloride equivalent to either 150 mg or 300 mg ranitidine) are supplied as follows:

150 mg: Beige, round, unscored, film-coated tablets imprinted RUGBY and 4455. They are available in bottles of 60 (NDC 0536-4455-06), 100 (NDC 0536-4455-01), 180 (NDC 0536-4455-18), 500 (NDC 0536-4455-05) and 1000 (NDC 0536-4455-10), and in unit dose packs of 100 (NDC 0536-4455-21).

300 mg: Beige, capsule-shaped, unscored, film-coated tablets imprinted RUGBY and 4456. They are available in bottles of 30 (NDC 0536-4456-07), 250 (NDC 0536-4456-02) and 500 (NDC 0536-4456-05), and in unit dose packs of 100 (NDC 0536-4456-21).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Dispense in a tight, light-resistant container as defined in USP/NF.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

Manufactured by
CHELSEA LABORATORIES, INC.
Cincinnati, Ohio 45215

Distributed by
RUGBY LABORATORIES, INC.
Norcross, GA 30071

Rev. 8/96

9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074864

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-864

3. NAME AND ADDRESS OF APPLICANT

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
8606 Reading Road
P.O. Box 15686
Cincinnati, OH 45215-0686

4. LEGAL BASIS FOR SUBMISSION

Page 06 includes a legal basis for submission statement. The firm references the Orange Book which lists Ranitidine Tablets 150 and 300 mg. Included are patent certification and Exclusivity statements on pages 09-12.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
Zantac Tablets

7. NONPROPRIETARY NAME
Ranitidine Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:
Date of Application 2/29/96
FDA acknowledgment letter 4/10/96
FDA Deficiency letter 8/13/96
Amendment response 10/11/96
FDA Deficiency Letter 3/6/97
Amendment Response 3/25/97
T-con dated 6/25/97
Fax amendment 6/27/97

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
150 mg and 300 mg

15. CHEMICAL NAME AND STRUCTURE
1,1-Ethenediamine, N-[2[[[5-[(dimethyl amino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-, monohydrochloride

16. RECORDS AND REPORTS
NA

17. COMMENTS
All deficiencies have been resolved.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is tentatively approvable.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
6/30/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074864

BIOEQUIVALENCE REVIEW(S)

ANDA 74-864

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
8606 Reading Road
P.O. BOX 15686
Cincinnati OH 45215-0686

JUN 14 1996

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on February 29, 1996, for Ranitidine Hydrochloride Tablets USP, 150 mg (base) and 300 mg (base).

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Please submit the sample, standard and QC preparation, and processing procedure. The complete analytical methodology should be submitted to include all aspects of sample handling, not just the description.

2. The actual blood drawing times were omitted from the raw data and should be submitted.

3.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Ranitidine HCl
150 mg & 300 mg tablet
-as base equivalent
NDA #74-864
Reviewer: J. Lee
74864SDW.296

JUN 5 1996

Chelsea Laboratories, Inc.
Cincinnati, Ohio
Submission date:
February 29, 1996

Review of an in-vivo Bioavailability Study, Dissolution Testing Data, and a Request for Waiver

Objective:

To assess the rate and extent of absorption of two ranitidine HCl formulations (Chelsea product vs Zantac®) after administration of single doses to subjects under fasted conditions.

Study Design:

The clinical study (019-92-1094) was conducted at
under the supervision of Principal Investigator, and
, Project Director.

Twenty-six male/female volunteers between the ages of 18-50 years and within 15% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry and urinalysis].

Those with any of the following conditions were excluded:

History of:

- asthma, serious cardiovascular, hepatic, renal, hematopoietic, GI or serious ongoing infectious diseases
- alcohol or drug abuse
- allergy to ranitidine, or to related drugs

Rx medications (excluding contraceptives) and OTC medications (excluding acetaminophen, vitamins) were not allowed within 14 days/7 days, respectively, of the first drug administration. There was to be no alcohol or caffeine consumption at least 24 and 12 hours, respectively, prior to drug administration.

Pregnant or nursing women volunteers were excluded at screening. Urine pregnancy tests were additionally performed for women volunteers at check-in for each phase.

The study was designed as a randomized, two-treatment, two-period, two-sequence crossover study with a one week washout period between dosings. Treatments consisted of a single 300 mg dose of the following:

A. Ranitidine HCl
300 mg tablet, batch #R57006
Chelsea Laboratories, Inc.
expiry date: not given

B. Zantac®
300 mg tablet, batch #5ZPY089
Glaxo Pharmaceuticals
expiry date: May, 1997

Twenty-six subjects were dosed according to the following schedule:

	Period I 12/04/95	Period II 12/11/95
sequence I	A	B
sequence II	B	A

sequence I - subj. #2, 3, 6, 7, 9, 11, 14, 16, 17, 20, 22*, 24, 25
sequence II - subj. #1, 4, 5, 8, 10, 12, 13, 15, 18, 19, 21, 23, 26

One subject (#22) withdrew voluntarily from the study after completing period I.

After an overnight fast, subjects were given a 300 mg dose of ranitidine HCl with 240 ml of water. Fasting continued for 5 hours post-dose. Blood samples (10 ml) were drawn in Vacutainers without anticoagulant at 0 (pre-dose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 20 hours. There was one sampling deviation noted in this study - subj. #20, period II (Ref.) had her 0.33 sample taken 5 minutes late. The actual time vs scheduled time calculation for AUC_{0-t} was 0.31%; therefore, her AUC calculations were based on the scheduled phlebotomy times.

Seven subjects reported experiencing 4 adverse events a total of 14 times. The four events (headache, lightheadedness, dizziness, nausea) were judged to have been possibly related to the study medication. Six were attributed to the test product; eight to the reference product. All were judged mild in severity. The adverse events summary is attached.

Only one minor analytical protocol deviation concerning centrifugation time was reported. This is unlikely to affect analytical results.

Analytical: [Not for release under FOI]

Data Analysis:

Serum data was analyzed by an analysis of variance procedure (SAS, version 6.08) and the F-test to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and serum level concentrations at each sampling time. Of the original twenty-six subjects enrolled in the study, one did not complete the crossover; twenty-five datasets were analyzed.

Results:

No statistically significant differences were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed for the major bioavailability parameters, except for C_{max} on the original scale. There was 2% difference between the test and reference formulations for serum levels of ranitidine in AUC_{0-t} and AUC_{inf}. The Chelsea product produced a 3% higher C_{max} than the Glaxo product. The 90% shortest confidence intervals for ranitidine, using least squares means, are presented below:

		90% CI
original scale	AUC_{0-t} (n=25)	[95; 109]
	AUC_{inf} (n=25)	[95; 109]
	C_{max} (n=25)	[91; 114]
ln-transformed scale	AUC_{0-t} (n=25)	[94; 111]
	AUC_{inf} (n=25)	[94; 111]
	C_{max} (n=25)	[91; 119]

Mean serum level data and pharmacokinetic summary are attached.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study,

using the current USP dissolution method. The resultant summaries are attached.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Chelsea product was 100.2% of label claim; range = 96.6% - 101.8% (1.4% CV).

Batch Size:

The executed batch record for the bio-batch of Chelsea's 300 mg ranitidine HCl shows a yield of approximately dosage units.

Waiver Request:

The sponsor has requested a waiver of in-vivo requirements for their 150 mg ranitidine HCl tablet. A quantitative formulation comparison between the 150 mg and 300 mg tablet was submitted, and comparative dissolution testing results were provided between the company's 150 mg test product vs Zantac® 150 mg tablet.

Comment:

1. The company did not submit the sample, standard and QC preparation and processing procedure. The company should submit the complete analytical methodology to include all aspects of sample handling, not just the description.

2. The company has omitted actual blood draw times for the subjects in the raw data. The company should submit this information.

3.

Recommendation:

1. The fasting bioequivalence study conducted by for Chelsea Laboratories, Inc. on its ranitidine HCl 300 mg tablet, batch #R57006, comparing it to Zantac 300 mg tablet has been found incomplete per comments #1-3.

All comments should be transmitted to the company.

6/3/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR for 96

USP XXIII Apparatus II Basket _____ Paddle x rpm 50

Medium: water @ 37°C Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Zantac® 300 & 150 mg tablet

Assay Methodology: _____

Results

300 mg

Time (min)	Test Product Lot # R57006 Mean % Dissolved	Range	(CV)	Reference Product Lot # 5ZPT089 Mean % Dissolved	Range	(CV)
10	45.1	-	(4.6)	55.4	-	(7.6)
20	73.5	-	(12)	82.1	-	(3.8)
30	91.4		(4.6)	89.8	-	(4.0)
45	95.3		(2.7)	93.8	-	(3.3)
60	97.0		(2.1)	96.0	-	(2.4)
			( )			( )

150 mg

	Test Product Lot # R57005 Mean % Dissolved	Range	(CV)	Reference Product Lot # 5ZPT108 Mean % Dissolved	Range	(CV)
10	49.4	-	(4.0)	32.6	-	(15)
20	85.6	-	(9.4)	63.8	-	(16.9)
30	95.6	-	(4.8)	82.1	-	(10.2)
45	97.3	-	(3.1)	89.2	-	(5.5)
60	98.9	-	(2.3)	93.5	-	(3.9)
			( )			( )

TABLE 1: RANITIDINE SERUM CONCENTRATIONS (ng/ml)
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 25)
#019-92-10941

Time (Hours)	Chelsea Test Product	Glaxo Reference Product	Ratio Test/Reference	Significance
0	0.0000	0.0000	--	--
0.33	157.5 ± 91.83	116.3 ± 75.46	1.35	p<0.05
0.67	505.7 ± 212.1	415.0 ± 165.5	1.22	p<0.05
1	645.8 ± 367.2	554.3 ± 216.2	1.17	N.S.
1.33	735.7 ± 456.0	663.2 ± 286.5	1.11	N.S.
1.67	856.1 ± 565.7	829.3 ± 508.5	1.03	N.S.
2	990.2 ± 551.7	868.9 ± 461.1	1.14	N.S.
2.5	1036 ± 486.5	927.3 ± 483.6	1.12	N.S.
3	923.4 ± 347.8	896.5 ± 412.8	1.03	N.S.
3.5	802.4 ± 268.4	826.1 ± 345.0	0.97	N.S.
4	700.0 ± 238.6	742.4 ± 319.9	0.94	N.S.
5	503.2 ± 163.6	539.6 ± 223.0	0.93	N.S.
6	378.0 ± 135.6	391.9 ± 132.7	0.96	N.S.
8	209.1 ± 60.12	212.0 ± 62.93	0.99	N.S.
10	114.9 ± 37.64	113.9 ± 39.69	1.01	N.S.
12	61.26 ± 20.75	63.01 ± 24.96	0.97	N.S.
16	22.54 ± 10.34	20.58 ± 10.54	1.10	N.S.
20	6.012 ± 8.479	6.116 ± 8.398	0.98	N.S.

TABLE 2: PHARMACOKINETIC PARAMETERS
ARITHMETIC MEANS ± STANDARD DEVIATION (N = 25)
SERUM RANITIDINE
#019-92-10941

Parameter	Test: Chelsea N	Mean ± Std. Dev.	C.V.	Reference: Glaxo N	Mean ± Std. Dev.	C.V.	Test/ Reference
AUC 0-T (ng ml^{-1}hr)	25	5268 ± 1431	27.2	25	5146 ± 1460	28.4	1.02
Ln AUC 0-T Geometric Mean	25	8.5293 ± 0.2988 5061		25	8.5006 ± 0.3217 4918		1.03
AUC 0-Inf (ng ml^{-1}hr)	25	5331 ± 1429	26.8	25	5205 ± 1461	28.1	1.02
Ln AUC 0-Inf Geometric Mean	25	8.5423 ± 0.2944 5127		25	8.5134 ± 0.3163 4981		1.03
Cmax (ng/ml)	25	1312 ± 532.9	40.6	25	1266 ± 518.9	41.0	1.04
Ln Cmax Geometric Mean	25	7.0876 ± 0.4562 1197		25	7.0365 ± 0.5143 1137		1.05
Tmax (hr)	25	2.427 ± 0.8385	34.5	25	2.494 ± 0.8705	34.9	0.97
Rate Constant (hr^{-1})	25	0.2780 ± 0.05172	18.6	25	0.2831 ± 0.04624	16.3	0.98
Half-Life (hr)	25	2.586 ± 0.5378	20.8	25	2.518 ± 0.4606	18.3	1.03
Cmax/ AUCI	25	0.2402 ± 0.05955	24.8	25	0.2360 ± 0.06024	25.5	1.02
Ln (Cmax/AUCI) Geometric Mean	25	-1.4546 ± 0.2407 0.2335		25	-1.4769 ± 0.2672 0.2283		1.02

TABLE 3: PHARMACOKINETIC PARAMETERS
LEAST SQUARES MEANS ± STANDARD ERROR (N = 25)
SERUM RANITIDINE
#019-92-10941

Parameter	Test Chelsea	Reference Glaxo	Test/ Reference	Significance	Study Power	Intrasubject C.V.(%)	90% Confidence Interval
AUC 0-T (ng ml^{-1}hr)	5246 ± 152.4	5150 ± 152.4	1.02	N.S.	0.99	14.8	0.95; 1.09
Ln AUC 0-T (Antiln)	8.5245 ± 0.0349 (5037)	8.5011 ± 0.0349 (4920)	1.02	N.S.	0.97	17.6	0.94; 1.11
AUC 0-Inf (ng ml^{-1}hr)	5309 ± 152.0	5209 ± 152.0	1.02	N.S.	0.99	14.6	0.95; 1.09
Ln AUC 0-Inf (Antiln)	8.5376 ± 0.0344 (5103)	8.5138 ± 0.0344 (4983)	1.02	N.S.	0.97	17.3	0.94; 1.11
Cmax (ng/ml)	1300 ± 61.86	1266 ± 61.86	1.03	N.S.	0.79	24.4	0.91; 1.14
Ln Cmax (Antiln)	7.0779 ± 0.0561 (1185)	7.0361 ± 0.0561 (1137)	1.04	N.S.	0.67	28.6	0.91; 1.19
Tmax (hr)	2.425 ± 0.1424	2.493 ± 0.1424	0.97	N.S.	0.66	28.5	0.83; 1.11
Rate Constant (hr^{-1})	0.2777 ± 0.00621	0.2833 ± 0.00621	0.98	N.S.	>0.99	11.0	0.93; 1.03
Half-Life (hr)	2.590 ± 0.06539	2.516 ± 0.06539	1.03	N.S.	>0.99	13.0	0.97; 1.09
Cmax/ AUCI	0.2389 ± 0.00800	0.2358 ± 0.00800	1.01	N.S.	0.98	16.9	0.93; 1.10
Ln (Cmax/AUCI) (Antiln)	-1.4598 ± 0.0336 (0.2323)	-1.4777 ± 0.0336 (0.2282)	1.02	N.S.	0.98	16.9	0.94; 1.10

The test of equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant (α=0.05), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

Figure 1: Mean Ranitidine Serum Levels

#019 – 92 – 10941

N = 25

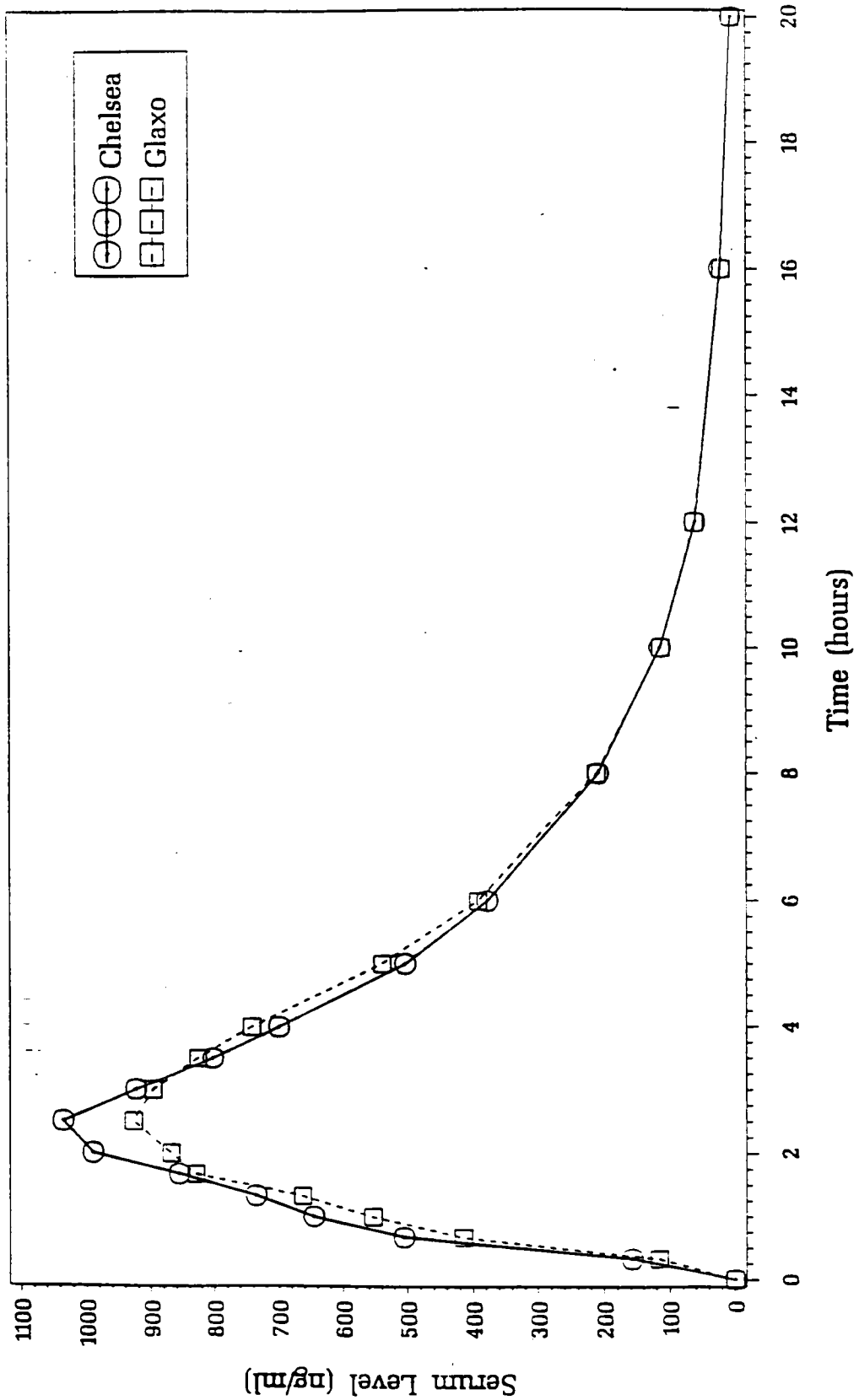

TABLE 1: DEMOGRAPHIC INFORMATION
RANITIDINE HCL TABLETS, 300 MG
#019-92-10941

SUBJECT	INITIALS	DATE OF BIRTH	AGE	RACE[1]	GENDER[2]	FRAME SIZE[3]	HEIGHT(IN.)	WEIGHT(LBS.)
1		10/21/72	23	B	M	M	70	177
2		11/27/50	45	B	M	S	78	173
3		08/02/58	37	C	M	M	71	173
4		01/21/66	29	B	M	M	75	202
5		04/03/53	42	B	M	M	70	180
6		01/09/67	28	B	M	M	71	152
7		07/04/67	28	B	F	M	66	164
8		08/30/53	42	C	F	M	63	119
9		09/27/77	18	C	F	M	67	169
10		10/08/76	19	C	F	M	64	106
11		12/29/70	24	C	F	M	63	134
12		09/29/74	21	B	F	L	67	154
13		06/27/67	28	B	F	M	65	138
14		05/16/58	37	B	F	M	68	157
15		05/28/75	20	B	F	M	65	135
16		04/10/53	42	B	F	M	64	128
17		09/23/77	18	B	F	M	62	126
18		02/21/62	33	B	F	M	67	146
19		04/17/69	26	B	F	M	63	131
20		08/04/54	41	B	F	M	67	164
21		03/01/69	26	C	F	S	65	120
22		04/15/73	22	C	F	M	62	130
23		12/30/67	27	B	F	M	61	122
24		12/29/62	32	B	F	M	66	117
25		10/26/76	19	B	F	M	66	158
26		01/29/47	48	C	F	L	64	170

[1] B = BLACK, C = CAUCASIAN
[2] M = MALE, F = FEMALE
[3] S = SMALL, M = MEDIUM, L = LARGE

TABLE 3: SAMPLE SCHEDULE DEVIATIONS
RANITIDINE HCL TABLETS, 300 MG
#019-92-10941

SUBJECT#	PERIOD	TIME POINT	SCHEDULED TIME	ACTUAL TIME	DEVIATION
20	II	0.33 hour	09:58	10:03	5 Minutes late

TABLE 5: ADVERSE EVENT
RANITIDINE HCL TABLETS, 300 MG
#019-92-10941

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	RX	PRODUCT UNDER STUDY
1	12/04/95	1030	Lightheaded	Mild	12/04/95 1230	Possible	Monitor	Glaxo
3	12/04/95	1130	Headache	Mild	12/04/95 1700	Possible	Monitor	Chelsea
	12/11/95	1200	Headache	Mild	12/11/95 1708	Possible	Monitor	Glaxo
17	12/11/95	0100	Headache	Mild	12/11/95 1730	Possible	Monitor	Chelsea
	12/11/95	1030	Dizziness	Mild	12/11/95 1730	Possible	Monitor/ fluids	Glaxo
18	12/11/95	1300	Dizziness	Mild	12/11/95 1630	Possible	Monitor/ fluids	Chelsea
	12/11/95	1730	Headache	Mild	12/11/95 2330	Possible	None	Chelsea
20	12/04/95	1300	Headache	Mild	12/05/95 0530	Possible	Monitor	Chelsea
	12/11/95	1230	Dizziness	Mild	12/11/95 1700	Possible	Monitor/ fluids	Glaxo
21	12/04/95	Early afternoon	Headache	Mild	12/05/95 0530	Possible	Monitor	Glaxo
	12/05/95	0900	Headache	Mild	12/05/95 1800	Possible	None	Glaxo
	12/11/95	1000	Headache	Mild	12/12/95 0200	Possible	Monitor	Chelsea
25	12/11/95	1230	Headache	Mild	12/11/95 1700	Possible	Monitor	Glaxo
	12/11/95	1230	Nausea	Mild	12/11/95 1630	Possible	Monitor	Glaxo

21. Bioavailability/Bioequivalence

c. Comparative Formulation Statement

The following Comparative Formulation Statement of the Chelsea Ranitidine Tablets, 150 mg and 300 mg demonstrates the proportionality of the active and inactive ingredients in the tablets of the 150 mg, to that of the 300 mg strength.

Comparative Formulation Statement
Ranitidine Tablets, 150 mg and 300 mg

Ingredients	150 mg %W/W	150 mg mg/tablet	300 mg %W/W	300 mg mg/tablet
Core				
Active Ingredient: Ranitidine HCl	61.09	168.0 mg	61.09	336.0 mg
Inactive Ingredients: Silicon Dioxide,				
Cellulose Microcrystalline				
Sodium Bicarbonate				
Talc				
Magnesium Stearate				
Total Weight (uncoated)	100.00	275.0 mg	100.00	550.0 mg
Coating				
Beige				
Beige				
Purified Water, USP**				
Clear				
Clear				
Purified Water, USP**		**		**
Total Weight (coated)		286.0 mg		572.0 mg

* Quantities indicated are theoretical weight gains for the tablet core after coating.
** Will be used in the process, but evaporated during coating operation.

ANDA 74-864

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle, Ph.D.
8606 Reading Road
Cincinnati OH 45215

JAN 15 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ranitidine Hydrochloride Tablets USP, 150 mg (base) and 300 mg (base).

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 2 1997

Ranitidine HCl
150 mg & 300 mg tablet
-as base equivalent
NDA #74-864
Reviewer: J. Lee
74864O.796

Chelsea Laboratories, Inc.
Cincinnati, Ohio
Submission date:
July 3, 1996

Review of a Study Amendment

This submission responds to deficiencies conveyed to the company on its bio-study for ranitidine 300 mg tablet.

1. Analytical Method

   The sample, standard, QC preparation and processing procedure, which was omitted from the original study report, has been submitted, as requested.

2. Actual Blood Draw Times

   The actual blood draw record was submitted as requested. The record shows that, of the deviations from the scheduled blood draw times, the worst case represented only a 0.31% difference in AUC (as noted in the original review of the study). All other sampling deviations were inconsequential in the calculation of AUC values.

3. Explanation

   7

Comment:

1. All deficiencies have been satisfactorily addressed.

Recommendation:

1. The bioequivalence study conducted by PharmaKinetics Laboratories for Chelsea Laboratories, Inc. on its ranitidine HCl 300 mg tablet , batch #R57006, comparing it to Zantac® 300 mg tablet, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Chelsea's test product is bioequivalent to the reference product, Zantac® manufactured by Glaxo Pharmaceuticals .

2. The in-vitro dissolution testing data on both the 150 mg and 300 mg tablet using the USP method, is also acceptable. The formulation for the 150 mg tablet is proportionally similar to the 300 mg tablet, which underwent a bioequivalence study. The waiver of in-

vivo study requirements for the 150 mg tablet is granted. Chelsea's ranitidine HCl ~~300~~ 150 mg tablet is deemed bioequivalent to Zantac® ~~300~~ 150 mg tablet manufactured by Glaxo Pharmaceuticals..

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

Not less thar of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

4. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

12/13/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 12/17/1996

Concur: _____ Date: 1/2/97

Rabi Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

JLee/jl/12-04-96

cc: NDA #74-864 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File